REMARKS

Claims 1-3 and 6-14 were pending before the Office. Claims 1 and 14 are hereby amended. Claims 6-8 are withdrawn. Accordingly, claims 1-3 and 6-14 will be pending upon entry of this paper.

No new matter is added by this amendment.

The amendments are made solely to claim more fully the invention and/or to expedite prosecution of the present application and should in no way be construed as an acquiescence to any of the Examiner's suggestions regarding prior art in the Office Action issued in the present application. Applicants reserve the right to pursue the subject matter of the claims as originally filed or similar claims in one or more subsequent applications.

Support for the amendments can be found throughout the originally-filed application, including the specification, drawings, examples and claims.

The rejection under 35 U.S.C. 102(e) is overcome

The Office Action rejects claims 1, 2 and 14 under 35 U.S.C. 102(e) as allegedly being anticipated by U.S. Published Application No. 2004/0009126 A1 to Pilkiewicz et al. ("PILKIEWICZ"). More in particular, the Examiner contends that PILKIEWICZ teaches "a method of treating [a] bacterial lung infection comprising local administration of ciprofloxacin by inhalation, wherein the ciprofloxacin is in the form of a particle and may be in the form of dry powder." The Examiner cites particularly to paragraphs [0064] and [0069]. Applicants respectfully disagree with the rejection and traverse as follows.

M.P.E.P § 2131 states that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art

reference." *See Verdegaal Bros. V. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987) (emphasis added). Moreover, the prior art must contain an enabling disclosure for a Section 102 rejection to stand. *See Chester v. Miller*, 15 U.S.P.Q.2d 1333, 1336 (Fed. Cir. 1990). "A claimed reference cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled." *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354 (Fed. Cir. 2003). A reference contains an enabling disclosure if a person of ordinary skill in the art could have combined the description of the invention in the prior art reference with his own knowledge of the art to have placed himself in possession of the invention. *See, e.g. Id.* At 1354 and *In re Donohue,* 226 U.S.P.Q. 619, 621 (Fed. Cir. 1985). Moreover, an invention described in a prior art publication cannot anticipate wherein that prior art invention is inoperable. *See, e.g., U.S. v. Adams*, 383 U.S. 39 (S. Ct. 708) (1966), citing *Smith v. Snow*, 204 U.S. 1 (S. Ct. 279) (1935) ("An inoperable invention or one which fails to achieve its intended result does not negative novelty").

Respectfully, as is argued further below, PILKIEWICZ does not teach, either expressly or inherently, each and every element of the presently claimed invention because it at least does not teach or suggest the solid betaine form of formula III. Instead, its teachings are limited to the standard compound, ciprofloxacin hydrochloride, which is inline with the same prior art over which the present invention improves upon. Even if PILKIEWICZ were viewed, *arguendo,* as containing a teaching of the solid betaine form of ciprofloxacin, PILKIEWICZ would not be operable as to the present invention because its data shows that a free ciprofloxacin formulation is neglibibly deliverable to lung tissue in

model mice, thereby failing to achieve its intended result, in contrast to the liposomal ciprofloxacin formulation of PILKIEWICZ, which purportedly showed good deliverability. Thus, PILKIEWICZ's own data suggest the inoperability of delivering ciprofloxacin as a free compound, unlike what is claimed and shown to be effective by the present invention. Accordingly, Applicants request reconsideration and withdrawal of the Section 102 rejection.

In more detail, claim 1 recites a method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of formula (III) (free ciprofloxacin or enrofloxacin in a betaine form) or its solid slightly soluble salt, wherein R = H (ciprofloxicin), C_2H_5 (enrofloxacin) and, wherein the solid betaine or its solid slightly soluble salt is administered in a powder form or powder-containing suspension.

Applicants do not contest that ciprofloxacin has been known for many years. Indeed, ciprofloxacin (specifically, ciprofloxacin hydrochloride) was first developed by the Assignee more than 20 years ago as a broad spectrum fluoroquinolone antibiotic and is trademarked as Cipro® (ciprofloxacin hydrochloride). See Physicians's Desk Reference, Edition 61 (2007), pp.1000, a copy of which is enclosed. This state of the art is reflected in the application at page 2, wherein it provides the chemical formula of ciprofloxacin hydrochloride. In contrast to the prior art, the present invention concerns not the hydrochloride form of ciprofloxacin, but rather the free, solid betaine form of ciprofloxacin and enrofloxacin. The specification teaches that "[i]t has been found, surprisingly, that control of diseases of the respiratory organs, especially lung diseases caused by bacteria, is

extremely successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt. The active ingredient concentration in the lungs can be kept for a lengthy period at a level desirable from the medical viewpoint for optimal treatment. Besides the higher and long-lasting active ingredient level at the site of the infection, it is possible to achieve simultaneously a comparatively low systemic concentration of the active ingredient, so that side effects of the medication and the disquieting development of resistance through systemic selection pressure are at least drastically reduced or even entirely prevented in this way."

The application also demonstrates in the Examples that the intratracheal use of ciprofloxacin betaine provides a significant improvement over the use of equivalent dosages of ciprofloxacin hydrochloride in the clearing of microorganisms from the lungs of test rats. See page 8-9. In addition, the Examples demonstrate that intratracheal administration of betaine ciprofloxacin provides significantly improved pharmacokinetic parameters (e.g., AUC, C_{max}) over the conventional ciprofloxacin hydrocholoride as determined by the amount of active ingredient could be detected in the lungs following intratracheal delivery. See page 8.

PILKIEWICZ at no point specifically teaches or even suggests the use or preparation or administration of the solid betaine form of ciprofloxacin. Instead, PILKIEWICZ relates generally to inhalation forms of antiinfective agents which are formulated with lipids or polymers. The reference indicates that its delivery formulations can be used with a whole host of different antiinfective agents, one of which purportedly can be "ciprofloxacin." See paragraph [0031]. Then, in Example 2, PILKIEWICZ talks about testing its liposomal

formulation with "Cipro Stock" against the "free" Cipro Stock, i.e., without the lipid formulation. There is nothing in PILKIEWICZ to suggest that its reference to "ciprofloxacin" and to "Cipro Stock" is none other than the ciprofloxacin hydrochloride form already available in the art. The term "Cipro" itself, which is used in Example 2 of PILKIEWICZ, is the trademark referring to the prior art solid product ciprofloxacine hydrochloride, which would seemingly have been used to prepare the stock solutions in Example 2. See Physicians's Desk Reference, Edition 61 (2007), pp.1000 (enclosed). It is believed that the present inventors, for the first time, have made the surprising finding that an entirely different form of ciprofloxacin—the betaine form—is advantageous over the standard ciprofloxacin hydrochloride form if delivered as a solid or as a slightly soluble salt form to the lungs of patients as a new approach for combating infectious diseases of the respiratory organs.

Even if PILKIEWICZ were viewed, *arguendo,* as containing a teaching of the solid betaine form of ciprofloxacin, which it does not, PILKIEWICZ would not be operable as to the present invention because its data shows that a free ciprofloxacin formulation is poorly deliverable to lung tissue in model mice, in contrast to its liposomal ciprofloxacin formulation of PILKIEWICZ, which purportedly showed good deliverability. See Example 2. Indeed, PILKIEWICZ concludes in view of the data of its Example 2 that "[o]nly liposomal ciprofloxacin delivered intratracheally was detectable in the lungs after 24 hours. Thus liposomal ciprofloxacin given by inhalation is more advantageous with respect to targeting and retention in the lung than free ciprofloxacin given either by inhalation or orally." See paragraph [0059]. Moreover, Example 2 states that the level of "free

ciprofloxacin delivered IT [intratracheally] was negligible after one hour" and that "[o]nly liposomal ciprofloxacin administered by IT administration was detectable in the lungs after 24 hours." Thus, even if the ciprofloxacin of PILKIEWICZ constituted a teaching of the betaine form of ciprofloxacin, which it does not, PILKIEWICZ's own experiments would have demonstrated to one of ordinary skill in the art that the delivery of free ciprofloxacin—i.e., without its liposomal formulation—would have been inoperable. It is noted also that the claim requires the "local administration of an antibacterially effective amount" of the solid betaine form, which would seem to further exclude PILKIEWICZ as an anticipating reference. A medical practitioner would certainly not be steered by PILKIEWICZ to administer anything other than a liposomal formulation of ciprofloxacin since the administration of free ciprofloxacin by its own showing is not sustained in the lungs and thus, would not be present to combat an infection. As noted above, inoperable inventions cannot be used to negate novelty.

For at least the above reasons, PILKIEWICZ does not anticipate the presently claimed invention. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

The rejections under 35 U.S.C. § 103 are overcome

The Examiner has rejected claims 1, 2 and 14 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Mayer et al. ("Clinical presentation of inhalational anthrax following bioterrorism exposure," Journal of the American Medical Association, November 28, 2001, Vol. 286, No. 20, pp. 2549-2553) ("MAYER") in view of Li et al. ("Ciprofloxacin-loaded bovine serum albumin microspheres: preparation and drug-release in

vitro," J. Microencapsulation, 2001, Vol. 19, No. 6, pp. 825-829) ("LI"). In addition, the Examiner has rejected claims 3 and 9-13 under 35 U.S.C. § 103(a) as allegedly being unpatentable over MAYER in view of LI and in further view of Grohe et al. (U.S. Patent No. 4,670,444) ("GROHE") and Vetter et al. (U.S. Patent No. 5,808,076 ("VETTER").

More in particular, the Examiner argues that the skilled artisan would have been motivated to modify MAYER, which relates to the intravenous administration of ciprofloxacin to anthrax lung infection patients, with the teachings of LI, which purportedly relates to the administration of ciprofloxacin by inhalation. The Examiner argues that the skilled artisan would have been motivated to make such a modification because, as noted in the Office Action, LI teaches that intravenous or oral administration of ciprofloxacin has "relatively unfavorable pharmacokinetic profile in the lower respiratory track."

Applicants respectfully disagree with the rejections and traverse as follows. For the reasons set forth below, neither MAYER nor LI, either taken alone or in combination, would have led one of ordinary skill in the art to make or use the instantly claimed invention. Neither GROHE nor VETTER cure the deficiencies of MAYER or LI.

As mentioned above, the present inventors have invented a new, useful and nonobvious method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of formula (III) (ciprofloxacin or enrofloxacin in betaine form) or its solid slightly soluble salt, wherein R = H (ciprofloxicin), C_2H_5 (enrofloxacin) and, wherein the solid betaine or its solid slightly soluble salt is administered in a powder form or powder-containing suspension. The invention is based on the surprising discovery that control of diseases of the respiratory

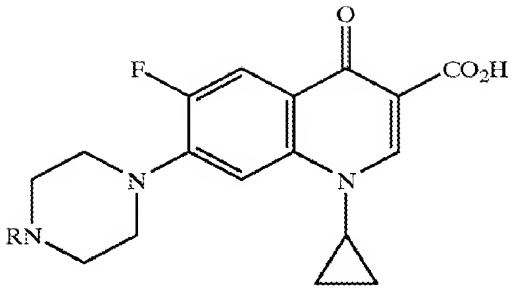
organs, especially lung diseases caused by bacteria, is extremely successful when ciprofloxacin or enrofloxacin is administered locally as solid betaine and/or as solid slightly soluble betaine salt.

MAYER relates to a report on the diagnosis and treatment of two rare cases of inhalation anthrax using a tri-therapy regimen of ciprofloxacin at 400 mg every 8 hours, rifampin at 300 mg every 12 hours, and clindamycin at 900 mg every 8 hours, each administered intravenously. MAYER merely reflects that which was already widely known in the art—namely, the intravenous delivery of ciprofloxacin for the treatment of anthrax. Unlike the present invention, MAYER has nothing to do with the local respiratory administration of solid ciprofloxacin, nor does it specifically teach the solid betaine form of ciprofloxacin. LI relates to a study reporting on the preparation and physical characterization (e.g., release rate of drug) of ciprofloxacin-encapsulated albumin microspheres for use in dry powder inhalers. In contrast with the invention, LI does not teach or suggest the specific use of the betaine form of ciprofloxacin. Instead, LI's reference to the trademark "CIPRO" as its source of ciprofloxacin suggests that LI uses none other than the standard ciprofloxacin hydrochloride, which is merely inline with the prior art over which the present invention has improved. See Physicians' Desk Reference, *supra.* Thus, neither MAYER or LI specifically teach the use or preparation of the solid betaine form of ciprofloxacin.

Even if, *arguendo*, MAYER or LI were viewed as constituting a teaching of the solid betaine form of ciprofloxacin, which is not admitted here, one of ordinary skill in the art would not be motivated to combine their teachings in the manner suggested by the Examiner

in view of the teaching away of PILKIEWICZ. As mentioned above, PILKIEWICZ suggests the inoperability of administering free ciprofloxacin and concludes that only liposomal formulations of ciprofloxacin—but not free ciprofloxacin—delivered intratracheally were detectable in the lungs after 24 hours. Armed with this knowledge, one of ordinary skill in the art would not have been motivated in any way to combine MAYER and LI to achieve the present invention. At best, one would have been possibly motivated to deliver the free ciprofloxacine of MAYER via the albumin microparticles of LI; however, no combination of MAYER with LI, in view of the teaching away of PILKIEWICZ, would have lead the ordinary skilled artisan to delivery free ciprofloxacin to the lungs since PILKIEWICZ shows such delivery to be inoperable. Thus, neither MAYER nor LI, either taken alone or in combination, teach or even fairly suggest the present invention.

Neither GROHE nor VETTER cure the deficiencies of either MAYER or LI. GROHE and VETTER are relied on by the Examiner for the elements of dependent claim 3 and 9-13, which are directed to particular salts of the compounds used in the base claim methods. Neither GROHE nor VETTER, either alone or in combination, teach or suggest the recited steps of the claimed invention, namely a method for controlling bacterial diseases of the respiratory organs in humans and animals by local administration of an antibacterially effective amount of solid betaine of the formula (III)



wherein R = H, C_2H_5 or its solid slightly soluble salt, wherein the solid betaine is administered in a powder form or powder-containing suspension. Instead, each of GROHE and VETTER relate merely to preparing salt variations of ciprofloxacin.

For at least the reasons above, the Examiner's conclusion of obviousness cannot stand. Indeed, other than impermissible hindsight, there is no convincing rationale for combining the cited prior art to achieve the presently claimed method that would support a conclusion of obviousness. Moreover, none of the cited references, considered alone or in any combination, in fact, teach the recited steps of the method of the invention as presently claimed.

Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the remarks made herein, the application is believed to be in condition for allowance. Favorable reconsideration of the application and prompt issuance of a Notice of Allowance are respectfully requested. Please charge any required fee or credit any overpayment to Deposit Account No. 04-1105.

Dated: January 24, 2009

Respectfully submitted,

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